EXHIBIT 14

Questions and Answers: Risk of oral clefts (cleft lip and/or palate) in infants born to mothers taking Topamax (Topiramate)

On March 4, 2011, the U.S. Food and Drug Administration (FDA) informed the public that new data show that infants born to women treated with topiramate (Topamax and generic products) during pregnancy have an increased risk for developing cleft lip or cleft palate (oral clefts).

Q1. What is Topamax (topiramate)?

Topiramate is an approved medication used to treat patients with epilepsy who have certain types of seizures. Topiramate is also approved for use to prevent migraine headaches, but not to relieve the pain of migraine headaches when they occur.[1]

Q2. Why is FDA warning patients about topiramate?

FDA has received new data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry that show an increased risk of oral clefts (cleft lip and/or palate) in infants who are exposed to topiramate during the first trimester of pregnancy. Similar findings have also been noted in another pregnancy registry in the United Kingdom. Oral clefts are defects in the formation of the upper lip and/or roof of the mouth. Oral clefts can affect the way a child's face looks, and can lead to problems with eating, talking, and/or ear infections. Most infants born with oral clefts undergo surgery to close the lip and/or palate during their first year of life.[2] Oral clefts happen early in pregnancy, before many women even know they are pregnant. Oral clefts also occur in infants whose mothers did not take topiramate or other medications during pregnancy, but they occur less often.

After considering the recent NAAED Pregnancy Registry data, FDA will be reclassifying topiramate as a **Pregnancy Category D drug**.

Q3. What should women do if they are currently taking topiramate?

Women taking topiramate should be aware that there is an increased risk of oral clefts in infants exposed to topiramate during the first trimester of pregnancy. Women of childbearing age should therefore talk to their healthcare professional about other treatment options. Women of childbearing age who do decide to continue taking topiramate and are not planning to become pregnant should use effective birth control. Because topiramate may cause certain birth control pills to work less well, women should talk to their health care providers about the best kind of birth control to use while they are taking topiramate. Women who become pregnant or are planning a pregnancy should talk to their healthcare professional right away to discuss whether continued use of topiramate is appropriate.

Women should not stop taking topiramate, even if they become pregnant, unless directed to do so by a healthcare professional. Stopping topiramate suddenly can cause serious problems.

All patients should report any side effects they experience while taking topiramate to FDA's MedWatch program using the "Contact Us" information at the bottom of this page.

Q4. What should pregnant women do if they are currently taking topiramate?

Pregnant women who are currently taking topiramate should immediately contact their healthcare professional to discuss the risks and benefits of continuing use of the drug. There may be alternate treatment options that are more appropriate for use during pregnancy that do not carry the increased risk of oral clefts or other birth defects. **Pregnant women should not stop taking topiramate unless directed to do so by a healthcare professional.** Stopping topiramate suddenly can cause serious problems. Not treating epilepsy during pregnancy can be harmful to women and their developing infants.

Pregnant women should also talk to their healthcare providers about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The NAAED Pregnancy Registry collects information about outcomes in infants born to women treated with antiepileptic drugs during pregnancy. Patients can enroll in this registry by calling 1-888-233-2334.

Q5. What should women do if they took topiramate during pregnancy?

Oral clefts are present at birth and cannot occur at a later date. If an infant was exposed to topiramate during pregnancy but was born without a cleft lip or palate, there is no chance of developing one after birth. There is still an increased risk for oral clefts in future pregnancies, however, if the mother continues to take topiramate Therefore, women of childbearing potential should talk to their healthcare professional about other treatment options. Women who decide to continue taking topiramate and are not planning to become pregnant again should use effective birth control. They should talk to their health care providers about the best kind of birth control to use, because topiramate may make certain birth control pills work less well.

Patients should know that topiramate passes into breast milk, and the effects of exposing infants to topiramate through breast milk are still unknown. Women who are currently breastfeeding while taking topiramate should talk to their healthcare professional about the best way to feed their infant while using this medication.

Q6. What does it mean when a drug is placed into "Pregnancy Category D"?

Some drugs approved by FDA as safe and effective for use in non-pregnant women may pose different and/or added risks to pregnant women and infants. To identify which drugs may have additional risks for babies born to pregnant women, FDA assigns all approved drugs to Pregnancy Categories based on data obtained through animal studies and clinical studies or experience. Pregnancy Categories also help patients and healthcare professionals weigh the risks and benefits of using a drug during pregnancy. Drugs in Pregnancy Category D have human data demonstrating evidence of human fetal risk, but the potential benefits of these drugs may still be considered acceptable in certain situations.[3]

Q7. Was FDA concerned about these potential safety issues when topiramate was approved?

Topiramate was previously classified as a Pregnancy Category C drug, which means that data from animal studies suggested potential fetal risks, but no adequate data from human clinical trials or studies were available at the time of approval. The topiramate labels are being updated with the new information describing the increased risk of oral clefts.

Q8. Does FDA have post marketing adverse event reports of oral clefts with topiramate?

There are reports of "cleft lip and cleft palate disorders" in the FDA's Adverse Event Reporting System (AERS) database with topiramate. AERS is a voluntary reporting system that receives reports from a variety of sources, including patients, physicians, pharmacists, other healthcare professionals, and pharmaceutical manufacturers. Data in the AERS database can generate information about possible risks associated with a medication. However in most situations, these reports cannot be used to show that a medication causes a specific birth defect or other unwanted effect (adverse event). For this reason, the data from the NAAED Pregnancy Registry were more helpful in determining a link between oral clefts and topiramate use. This registry has a built-in comparison group, which allowed FDA to compare the rates of oral clefts in infants exposed to topiramate with the rates of oral clefts in infants not exposed to topiramate.

1. U.S. National Library of Medicine. National Institutes of Health. Topiramate monograph. Available at**http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697012.html (http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697012.html)**. Accessed January 6, 2011.

2. U.S. National Library of Medicine. National Institutes of Health. Cleft Lip and Palate health topic. Available at **http://www.nlm.nih.gov/medlineplus/cleftlipandpalate.html (http://www.nlm.nih.gov/medlineplus/cleftlipandpalate.html)**. Accessed January 6, 2011.
3. Link to chart of FDA Pregnancy Categories - **http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf (http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf)**

Table 1. FDA Pregnancy Category Definitions

(language summarized from 21 CFR 201.57)

Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

Related Information

- **FDA Drug Safety Communication: Risk of oral clefts in children born to mothers taking Topamax (topiramate) (/Drugs/DrugSafety/ucm245085.htm)**
  3/4/2011

Contact FDA

1-800-332-1088
1-800-FDA-0178 Fax

Report a Serious Problem
MedWatch Online (https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm)
Regular Mail: Use postage-paid **FDA Form 3500 (http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf)**
Mail to: MedWatch 5600 Fishers Lane
Rockville, MD 20857

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Postmarket Drug Safety Information for Patients and Providers (/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm)

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Safe Use Initiative (/Drugs/DrugSafety/SafeUseInitiative/default.htm)

Drug Recalls (/Drugs/DrugSafety/DrugRecalls/default.htm)

Drug Supply Chain Integrity (/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/default.htm)